FORM PTO-1390 (REV 5-93)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY DOCKET NO. P101615-00007
	TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	DATE: September 19, 2000
		U.S. APPLN. NO. (IF KNOWN, SEE 37 CFR 1.5) 09/623506

INTERNATIONAL APPLICATION NO. PCT/EP99/01822	INTERNATIONAL FILING DATE 17 March 1999	PRIORITY DATE CLAIMED 27 March 1998

TITLE OF INVENTION: ACRYLOYL DERIVATIVES ANALOGOUS TO DISTAMYCIN, PROCESS FOR PREPARING THEM, AND THEIR USE AS ANTITUMOR AGENTS

APPLICANT(S) FOR DO/EO/US: Paolo COZZI, Pier Giovanni BARALDI, Italo BERIA, Marina CALDARELLI, Laura CAPOLONGO, Romeo ROMAGNOLI

1. XX This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
   (THE BASIC FILING FEE IS ATTACHED)

2. _ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. XX This express request to begin national examination procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT articles 22 and 39(1).

4. XX A proper demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. XX A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. XX is transmitted herewith (required only if not transmitted by the International Bureau).
   b. XX has been transmitted by the International Bureau.
   c. _ is not required, as the application was filed in the United States Receiving Office (RO/US)

6. _ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. _ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. _ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. _ have been transmitted by the International Bureau.
   c. _ have not been made; however, the time limit for making such amendments has NOT expired.
   d. _ have not been made and will not be made.

8. _ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. XX An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. _ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. XX An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. XX An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. XX A FIRST preliminary amendment.
    _ A SECOND or SUBSEQUENT preliminary amendment.

14. _ A substitute specification.

15. _ A change of power of attorney and/or address letter.

16. XX Other items or information: PCT/IPEA/409, PCT/IB/332, PCT/IB/308, PCT/IB/301, PCT/IB/304, PCT/ISA/210, Change of Name
    CHECK NO. 30112

U.S. APPLN. NO. (IF KNOWN, SEE 37 C.F.R. 1.5) 09/623506	INTERNATIONAL APPLICATION NO. PCT/E099/01822	ATTORNEY DOCKET NO. P101615-00007 DATE: September 19, 2000

17. XX The following fees are submitted: **Basic National Fee (37 CFR 1.492(a)(1)-(5):** Search Report has been prepared by the EPO or JPO.....$840.00 International preliminary examination fee paid to USPTO (37 CFR 1.482)..$670.00 No international preliminary examination fee paid to USPTO (37 CFR1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))....$760.00 Neither international preliminary examination fee (37 CFR 1.482) or international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....$970.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) .....$ 96.00	CALCULATIONS | PTO USE ONLY

ENTER APPROPRIATE BASIC FEE AMOUNT =				$840	
Surcharge of $130.00 for furnishing the oath or declaration later than _ 20 _ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$00	
Claims	Number Filed	Number Extra	Rate		
Total Claims	10 20 =	00	X $ 18.00	$00	
Independent Claims	01 - 3 =	00	X $ 78.00	$00	
Multiple dependent claim(s) (if applicable)			+ $260.00	$00	
TOTAL OF ABOVE CALCULATIONS =				$840	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$00	
SUBTOTAL =				$840	
Processing fee of $130.00 for furnishing the English translation later the _ 20 _ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$00	
TOTAL NATIONAL FEE =				$840	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +				$40	
TOTAL FEES ENCLOSED =				$880	
				Amount to be refunded	$
				Charged	$

a. XX A check in the amount of $880 to cover the above fees is enclosed.
b. _ Please charge my Deposit Account No. 01-2300 in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.
c. XX The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 01-2300 .

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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Robert B. Murray
Reg. No. 22,980

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Paolo COZZI et al

Serial No.: New Application

Filed: September 19, 2000

For: ACRYLOYL DERIVATIVES ANALOGOUS TO DISTAMYCIN, PROCESS FOR PREPARING THEM, AND THEIR USE AS ANTITUMOR AGENTS

PRELIMINARY AMENDMENT

Commissioner of Patents
Washington, D.C. 20231

September 19, 2000

Sir:

Prior to calculation of the filing fee and prior to the examination of this application, please amend the above-identified application as follows:

IN THE CLAIMS:

Claim 3, line 1, delete "or 2".

REMARKS

The above amendment to the claims has been made to correct the multiple dependency of the claims and to put the application in better condition for examination.

In the event that any fees are due in connection with this paper, please charge our Deposit Account No. 01-2300.

Respectfully submitted,
ARENT FOX KINTNER PLOTKIN & KAHN PLLC

Robert B. Murray
Attorney for Applicant
Reg. No. 22,980

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ACRYLOYL DERIVATIVES ANALOGOUS TO DISTAMYCIN, PROCESS FOR PREPARING THEM, AND THEIR USE AS ANTITUMOR AGENTS.

The present invention relates to new peptidic compounds analogous to Distamycin A, to a process for their preparation, to pharmaceutical compositions containing them and to their use as therapeutic agents.

Distamycin A is an antibiotic substance with antiviral and oncolytic properties, having a polypyrrole framework (Nature 203, 1064 (1964); J. Med. Chem. 32, 774-778 (1989)).

Several analogous to Distamycin A and derivatives thereof are known in the art.

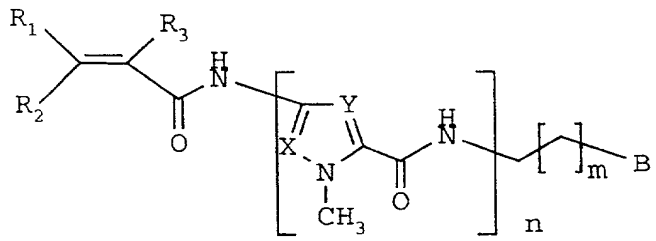
The international patent application WO 97/43258, in the name of the applicant, discloses acryloyl distamycin derivatives wherein the amidino moiety is replaced by different nitrogen-containing ending groups such as, for instance, cyanamidino, N-methylamidino, ethylguanidino, amido, amidoximo, nitrile and the like.

Distamycin derivatives wherein at least one pyrrole ring of the aforementioned polypyrrole framework is substituted by an imidazole or pyrazole ring are also reported in the literature.

See, for a general reference, Anti-Cancer Drug Design 8, 173-192 (1993); J. Am. Chem. Soc. Vol. 114, 5911-5919 (1992); Anti-Cancer Drug Design 6, 501-517 (1991); patent applications EP-A-0246868 and WO 96/05196, both in the name of the applicant.

It has now been found that a new class of distamycin derivatives as defined hereinunder, wherein at least one ring of the polypyrrole framework is other than pyrrole, the formyl group is substituted by an acryloyl moiety and the amidino group is substituted by different nitrogen-containing ending groups, shows valuable biological properties.

Therefore, the present invention provides compounds which are acryloyl substituted distamycin derivatives of formula



(I)

wherein:

n is 2, 3 or 4;

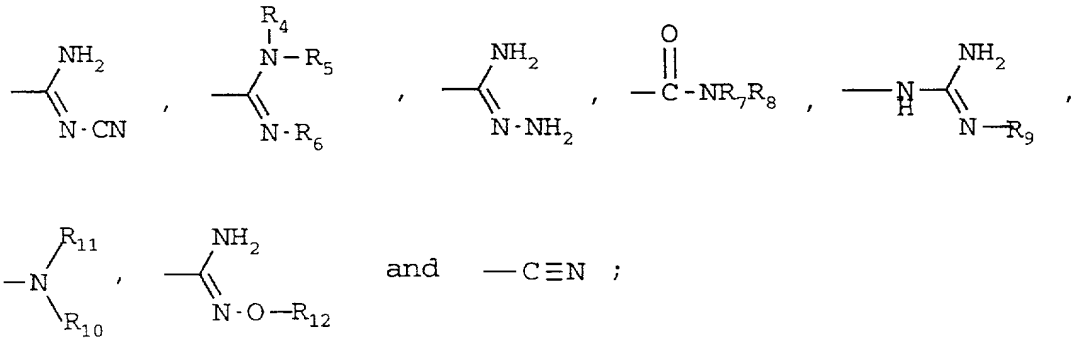
m is 1 or 2;

X and Y are the same or different and are selected, independently for each heterocyclic ring of the polyhetherocyclic chain, from N and CH;

R_1 and R_2, which are the same or different, are selected from hydrogen, halogen, and C_1-C_4 alkyl;

R_3 is hydrogen or halogen;

B is selected from



wherein R_4, R_5, R_6, R_7, R_8, R_{10}, R_{11} and R_{12} are, independently from each other, hydrogen or C_1-C_4 alkyl; and R_9 is hydrogen or hydroxy;

or a pharmaceutically acceptable salt thereof;

provided that

a) at least one of R_4, R_5 and R_6 is alkyl;

b) at least one of the heterocyclic rings within the polyheterocyclic chain is other than pyrrole; and

c) X and Y are not both N for the same heterocyclic ring.

The present invention includes within its scope also all the possible isomers covered by the compounds of formula (I), both separately and in admixture, as well as the

metabolites and the pharmaceutically acceptable bio-precursors (otherwise known as pro-drugs) of the compounds of formula (I).

In the present description, unless otherwise specified, the term alkyl includes straight or branched alkyl, for instance C_1-C_4 alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl; the term halogen includes fluorine, chlorine, bromine and iodine.

Preferably, the alkyl groups are selected from methyl and ethyl and the halogen atoms are selected from fluorine, chlorine or bromine.

Pharmaceutically acceptable salts of the compounds of formula (I) are the salts with pharmaceutically acceptable, inorganic or organic, acids. Examples of inorganic acids are hydrochloric, hydrobromic, sulphuric and nitric acid; examples of organic acids are acetic, propionic, succinic, malonic, citric, tartaric, methanesulfonic and p-toluenesulfonic acid.

As above reported, X and Y are selected, independently for each heterocyclic ring of the polyheterocyclic chain, between N and CH. This means that within the compounds of formula (I) and for different heterocyclic rings, X can be either N as well as CH; the same applies for Y provided that X and Y are not contemporaneously N for a single heterocycle.

Examples for the said heterocycles are pyrrole, pyrazole and imidazole.

A preferred class of compounds according to the present invention is represented by the compounds of formula (I) wherein R_4, R_5, R_6, R_7, R_8, R_{10}, R_{11} and R_{12} are, independently from each other, hydrogen, methyl, or ethyl.

Even more preferred are the compounds of formula (I) wherein

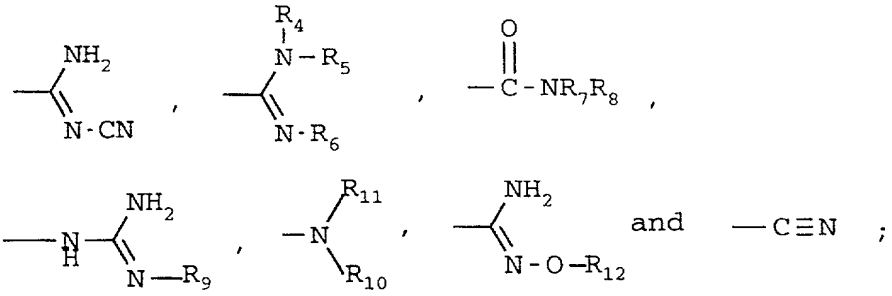
n is 3 or 4;

m is 1;

R_1 and R_2 are hydrogen;

R_3 is chlorine or bromine;

B is selected from



wherein R_4, R_5, R_6, R_7, R_8, R_{10}, R_{11} and R_{12} are, independently from each other, hydrogen or methyl; R_9 is hydrogen.

Another class of preferred compounds of formula (I) are those wherein the acrylamido moiety is directly linked to a pyrazole or imidazole ring.

Examples of specific compounds according to the present invention, especially in the form of salts, preferably with hydrochloric acid, are the following:

(1) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propioncyanamidine;

(2) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine;

(3) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine;

(4) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N'-dimethylamidine;

(5) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-

chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N'-dimethylamidine;

(6) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N,N'-trimethylamidine;

(7) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamide;

(8) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamide;

(9) 2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine;

(10) 2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine;

(11) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propyl-N,N-dimethylamine;

(12) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamidoxime;

(13) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propionamidoxime;

(14) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-O-methylamidoxime;

(15) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-O-methylamidoxime;

(16) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propionitrile;

(17) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propionitrile;

(18) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propioncyanamidine;

(19) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N-methylamidine;

(20) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N,N'-dimethylamidine;

(21) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N,N,N'-trimethylamidine;

(22) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-

carboxamido propionamide;

(23) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N-methylamide;

(24) 2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) ethylguanidine;

(25) 2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-chloroacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) ethylguanidine;

(26) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propyl-N,N-dimethylamine;

(27) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propionamidoxime;

(28) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-chloroacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propionamidoxime;

(29) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-O-methylamidoxime;

(30) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-chloroacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-O-methylamidoxime;

(31) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-

carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propionitrile;

(32) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N-methylamidine;

(33) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N-methylamidine;

(34) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N,N'-dimethylamidine;

(35) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N,N,N'-trimethylamidine;

(36) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N-methylamide;

(37) 2-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) ethylguanidine;

(38) 2-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) ethylguanidine;

(39) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propionamidoxime;

(40) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-

bromoacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propionitrile;

(41) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propioncyanamidine;

(42) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N-methylamide;

(43) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N,N-dimethylamine;

(44) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-O-methylamidoxime;

(45) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propionitrile;

(46) 3-(1-methyl-3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrazole-5-carboxamido)propion-N-methylamidine;

(47) 3-(1-methyl-3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrazole-5-carboxamido)propion-N,N'-dimethylamidine;

(48) 2-(1-methyl-3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrazole-5-carboxamido)ethylguanidine;

(49) 3-(1-methyl-3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrazole-5-carboxamido)propionamidoxime;

(50) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)imidazole-2-carboxamido)propion-N-methylamidine;

(51) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)imidazole-2-carboxamido)propionamide;

(52) 2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)imidazole-2-carboxamido)ethylguanidine;

(53) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)imidazole-2-carboxamido)propionamidoxime;

(54) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N-methylamidine;

(55) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N,N'-dimethylamidine;

(56) 2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) ethylguanidine;

(57) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-

carboxamido) propionamidoxime;

(58) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propionitrile;

(59) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propioncyanamidine;

(60) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine;

(61) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine;

(62) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N'-dimethylamidine;

(63) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N,N'-trimethylamidine;

(64) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamide;

(65) 2-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine;

(66) 2-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine;

(67) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-

carboxamido)pyrrole-2-carboxamido)propionamidoxime;

(68) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamidoxime;

(69) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionitrile;

(70) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propioncianamidine;

(71) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine;

(72) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N'-dimethylamidine;

(73) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N,N'-trimethylamidine;

(74) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamide;

(75) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamide;

(76) 2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine;

(77) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N-

dimethylamine;

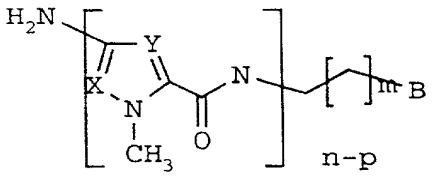
(78) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamidoxime;

(79) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-O-methylamidoxime;

(80) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionitrile.

The compounds of the present invention can be prepared according to one of the following processes, which comprise:

(a) reacting a compound of formula:

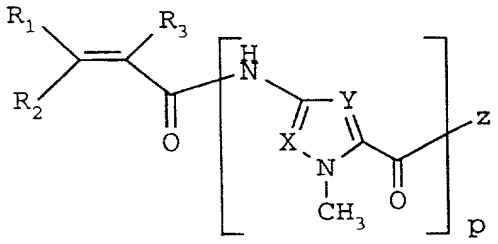


(II)

wherein n, m, X, Y and B are as defined above;

p is 0 or 1;

with a compound of formula:



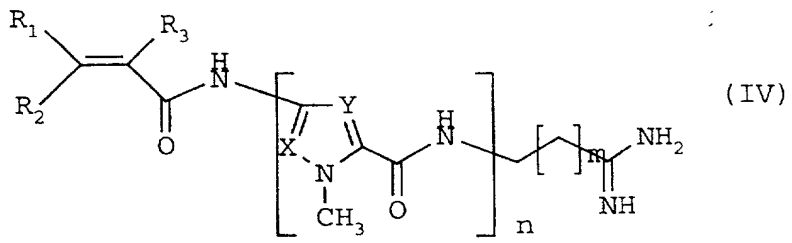
(III)

wherein R_1, R_2, R_3, X, Y and p are as defined above;

Z is hydroxy or a leaving group;

or:

(b) when B is equal to -C≡N, reacting a compound of formula:



(IV)

wherein n, m, R_1, R_2, R_3, X and Y are as defined above; with succinic anhydride; and

(c) if desired, converting a compound of formula (I) into a pharmaceutically acceptable salt thereof.

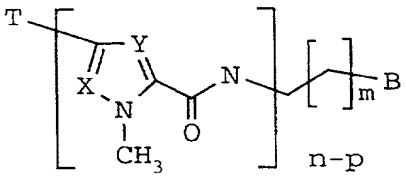
In the compounds of formula (III), Z is hydroxy or a suitable leaving group selected, for instance, among chloro, 2,4,5-trichlorophenoxy, 2,4-dinitro-phenoxy, succinimido-N-oxy, imidazolyl group, and the like.

The reaction of process (a) as above between a compound of formula (II) and a compound of formula (III) can be carried out according to known methods, for instance those described in the aforementioned EP-A-246,868 and WO 96/05196.

It is clear to the man skilled in the art that when preparing the compounds of formula (I) according to the process object of the present invention, optional amino groups, i.e. R_{10} and/or R_{11} of the compound of formula (II) equal to hydrogen, need to be properly protected according to conventional techniques, so as to avoid unwanted side reactions.

Likewise, the conversion of the said protected amino group into the free amine may be carried out according to known procedures. See, for a general reference, J. Org. Chem. 43, 2285, (1978); J. Org. Chem. 44, 811 (1979); J. Am. Chem. Soc. 78, 1359 (1956); Ber. 65, 1192 (1932); and J. Am Chem. Soc. 80, 1154, (1958).

The compounds of formula (II) may be prepared by converting the compounds of formula (V)

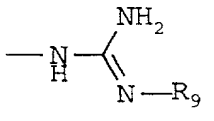


(V)

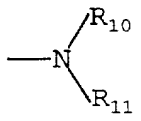
wherein T is a nitro group or an amino group properly protected with a group such as, for instance, t-butyloxycarbonyl, triphenylmethyl or, preferably, carbobenzyloxy or formyl; X, Y, B, n, m and p are as defined above; into the desired amino derivative of formula (II).

The conversion of the nitro group into amino group may be carried out according to known procedures such as, for instance, hydrogenation under hydrogen pressure in the presence of suitable catalysts, e.g., palladium on charcoal, into a suitable solvent such as dioxane, methanol, ethanol and mixtures thereof, at room temperature.

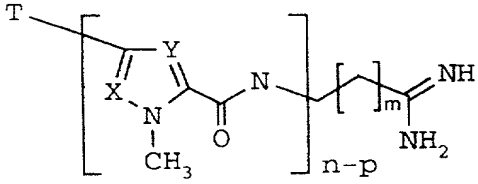
The compounds of formula (V) wherein B is other than



and



can be obtained, in their turn, from the compounds of formula:

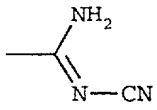


(VI)

wherein T, X, Y, n, p and m are as defined above;

by using:

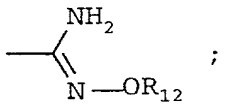
(i) H_2N-CN, so obtaining a compound of formula (V) having B equal to:



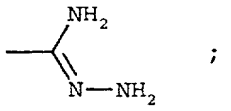
;

(ii) H_2N-OR_{12} wherein R_{12} has the above reported meanings, so obtaining a compound of formula (V) having B

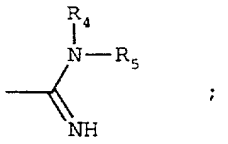
equal to:



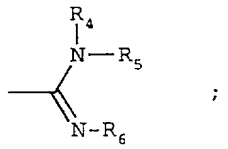
(iii) H_2N-NH_2, so obtaining a compound of formula (V) having B equal to:



(iv) HNR_4R_5, so obtaining a compound of formula (V) having B equal to:



and then optionally with H_2NR_6, so obtaining a compound of formula (V) having B equal to:

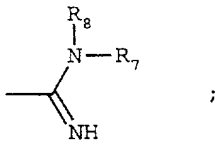


wherein R_4, R_5, and R_6 are as defined above;

(v) succinic anhydride, so obtaining a compound of formula (V) having B equal to -C≡N;

(vi) water in an alkaline medium, so obtaining a compound of formula (V) having B equal to $-CO-NR_7R_8$ wherein R_7 and R_8 are both hydrogen;

(vii) HNR_7R_8, so obtaining a compound of formula (V) having B equal to:

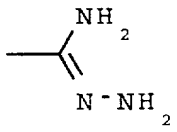


and then with water in an alkaline medium, so obtaining a compound of formula (V) having B equal to $-CO-NR_7R_8$, wherein R_7 and R_8 are as defined above.

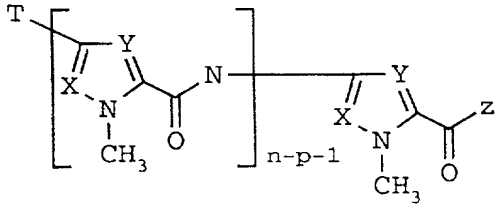
The reaction between a compound of formula (VI) and one of

the reactants as set forth in points (i)-(vii) as above can be carried out according to known methods, for instance those reported in WO97/43258; Chem. Revs. 1961; 155; J. Med. Chem. 1984, 27, 849-857; Chem. Revs. 1970, 151; and "The Chemistry of Amidines and Imidates", edited by S. Patai, John Wiley & Sons, N.Y. (1975).

Alternatively, the compounds of formula (V) wherein B is other than

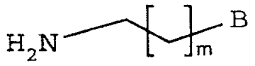


can be prepared from a compound of formula:



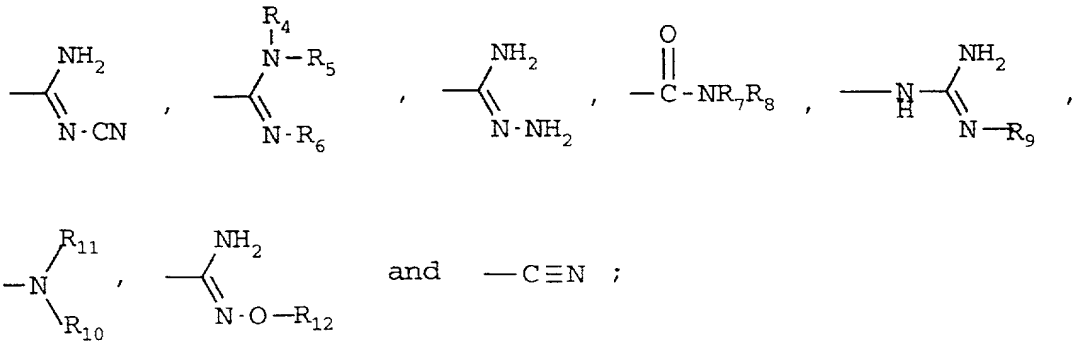
(VII)

wherein n, p, X, Y, T and Z are as defined above, by reaction with a compound of formula:



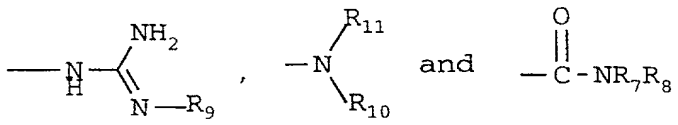
(VIII)

wherein m is as defined above and B is selected from:



wherein R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are as defined above.

Finally, the compounds of formula (V) wherein B is other than



can be prepared through the so-called Pinner reaction, by reacting a compound of formula (V) wherein B is equal to CN with a suitable amino compound as set forth above under points (i), (ii), (iii) or (iv).

Also the compounds of formula (III) are known or easily prepared according to conventional methods.

See, for a general reference, WO96/05196; J.C.S. 1947-1032 and JACS 62, 3495 (1940).

The reaction of process (b) is carried out according to the method reported in WO 97/43258.

The compounds of formula (IV), (VI), (VII) and (VIII) are known compounds, or may be obtained by known methods (see, for a general reference, Tetrahedron, 34, 2389-2391, 1978; J. Org. Chem., 46, 3492-3497, 1981; J. Org. Chem., 52, 3493-3501, 1987; WO96/05196 and WO97/43258.

The optional conversion of a compound of formula (I) into a pharmaceutically acceptable salt, as well as the preparation of a free compound starting from a salt, may be carried out by known standard methods.

Well known procedures such as, e.g., fractional crystallization or chromatography, may also be followed for separating a mixture of isomers of formula (I) into the single isomers.

The compounds of formula (I) may be purified by conventional techniques such as, e.g., silica gel or alumina column chromatography, and/or by recrystallization from an organic solvent such as, e.g., a lower aliphatic alcohol, e.g. methyl, ethyl or isopropyl alcohol, or dimethylformamide.

The compounds of the invention show cytotoxic properties towards tumor cells so that they can be useful as antineoplastic agents, e.g. to inhibit the growth of various tumors such as, for instance, carcinomas, e.g. mammary carcinoma, lung carcinoma, bladder carcinoma, colon

carcinoma, ovary and endometrial tumors. Other neoplasias in which the compounds of the invention could find application are, for instance, sarcomas, e.g. soft tissue and bone sarcomas, and the hematological malignancies such as, e.g., leukemias.

The antitumor activity of the compounds of formula (I) was evaluated in vitro by cytotoxicity studies carried out on murine L1210 leukemia cell. Cells were derived from in vivo tumors and established in cell culture. Cells were used until the tenth passage. Cytotoxicity was determined by counting surviving cells after 4 hours treatment and 48 hours growth in drug-free medium.

The percentage of cell growth in the treated cultures was compared with that of controls. Doses inhibiting 50% of the cellular growth in respect to controls, expressed as ID_{50} values, were calculated on dose-response curves.

The compounds of the invention can be administered by the usual routes, for example, parenterally, e.g. by intravenous injection or infusion, intramuscularly, subcutaneously, topically or orally.

The dosage depends on the age, weight and conditions of the patient and on the administration route.

For example, a suitable dosage for administration to adult humans may range from about 0.05 to about 100 mg pro dose 1-4 times a day.

The pharmaceutical compositions of the invention contain a compound of formula (I) as the active substance, in association with one or more pharmaceutically acceptable excipients.

The pharmaceutical compositions of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.

For instance, solutions for intravenous injection or infusion may contain sterile water as a carrier or, preferably, they may be in the form of sterile aqueous isotonic saline solutions.

Suspensions or solutions for intramuscular injections may

contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol and, if desired, a suitable amount of lidocaine hydrochloride.

In the form for topical application, e.g. creams, lotions or pastes for use in dermatological treatment, the active ingredient may be mixed with conventional oleaginous or emulsifying excipients.

The solid oral forms, e.g. tablets and capsules, may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch and potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethyl-cellulose, polyvinylpyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates, sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, for instance, lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in a known manner, for example by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

Furthermore, according to the present invention, there is provided a method of treating tumors in a patient in need of it, comprising administering to the said patient a composition of the invention.

The following examples illustrate but do not limit the invention.

The abbreviations DMF and DMSO-d_6 stand for dimethylformamide and deutero-dimethylsulfoxide, respectively.

Example 1

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromo acrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido) pyrrole-2-carboxamido)pyrrole-2-carboxamido) propioncyanamidine

Step I: The intermediate 1-methyl-3-(α-bromoacrylamido) pyrazole-5-carboxylic acid.

To a solution containing 0.620 g of ethyl 3-aminopyrazole-1-methyl-5-carboxylate and 0.3 g of 2-bromoacrylic acid in 10 ml of dioxane, 0.412 g of N-N'dicyclohexylcarbodiimide were added and the mixture was stirred at room temperature overnight. After filtration, the solvent was evaporated in vacuo, the solid residue was dissolved in 50 ml of ethyle acetate, treated with a saturated solution of sodium bicarbonate and then with 10% hydrochloric acid. The organic phase was dried over anhydrous sodium sulfate and the solvent evaporated in vacuo. The solid residue was purified by recrystallization from ethanol-water to yield 0.48 g of ethyl 1-methyl-3-(α-bromoacrylamido)-pyrazole-5-carboxylate. The derivative (0.48 g) was dissolved in 10 ml of dioxane and added of 1.6 ml of 2 N potassium hydroxide. The mixture was stirred overnight, acidified with 10% hydrochloric acid and the solvent was evaporated in vacuo yielding 0.40 g of intermediate.

PMR(DMSO-d_6) d: 12.9 (b.s., 1H), 10.1 (s, 1H), 7.22 (s, 1H), 6.95 (d, J=3.7Hz, 1H), 6.43 (d, J=3.7 Hz, 1H), 4.02 (s, 3H).

By analogous procedure the following compounds can be prepared:

1-methyl-4-(α-bromoacrylamido)pyrrole-2-carboxylic acid

PMR(DMSO-d_6) d: 12.2 (b.s., 1H), 10.2 (s, 1H), 7.38 (d, J=1.8 Hz, 1H), 6.85 (d, J=1.8 Hz, 1H), 6.68 (d, J=3.7 Hz, 1H), 6.2 (d, J=3.7 Hz, 1H), 3.82 (s, 3H);

1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxylic acid

PMR (DMSO-d_6) d: 11.08 (s, 1H), 7.58 (s, 1H), 6.82 (d, J=2.3 Hz, 1H), 6.29 (d, J=2.3.8 Hz, 1H), 3.81 (s, 3H);

1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxylic acid;

1-methyl-2-(α-chloroacrylamido)pyrrole-4-carboxylic acid

FAB-MS: m/z 228(40, $[M+H]^+$), 193, 139

PMR(DMSO-d_6) d: 12.20 (b.s., 1H), 10.24 (s, 1H), 7.39 (d, J=2.0 Hz, 1H), 6.88 (d, J=2.0 Hz, 1H), 6.37 (d, J=2.2 Hz, 1H), 5.99 (d, J=2.2 Hz, 1H), 3.81 (s, 3H);

1-methyl-4-(α-chloroacrylamido)imidazole-2-carboxylic acid.

Step II: The intermediate 1-methyl-3-(α-bromoacrylamido)pyrazole 5-carboxyl chlodride

The intermediate obtained from step I (1.2 g) was dissolved in 40 ml of benzene and added of 10 ml of $SOCl_2$. After refluxing for 1 hour the solution was evaporated to dryness in vacuo to give 1.4 g of the intermediate.

By analogous procedure and by using the opportune starting materials the following compounds can be obtained:

1-methyl-4-(α-bromoacrylamido)pyrrole-2-carboxyl chloride;

1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxyl chloride;

1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxyl chloride;

1-methyl-4-(α-chloroacrylamido)pyrrole-2-carboxyl chloride;

1-methyl-4-(α-chloroacrylamido)imidazole-2-carboxyl chloride.

Step III: The intermediate 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propioncyanamidine hydrochloride

To a solution of 324 mg of cyanamide in 20 ml of DMF 186 mg of sodium hydride were added. The mixture was stirred at room temperature for 30 min. and then added to a solution of 1 g of distamycin A in 10 ml DMF. The solution was stirred at room temperature for two hours and acetic acid was then added up to pH=7. The solvent was removed at reduced pressure and the crude residue purified by flash chromatography (methylene chloride/methanol:9/1) to give 900 mg of 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-

formamidopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propioncyanamidine which was dissolved in 50 ml of methanol and added with 5 ml of 2 N hydrochloric acid.

The reaction mixture was stirred at room temperature for two days, the solvent was evaporated in vacuo and the solid residue suspended in 200 ml of ethyl acetate, yielding after filtration 600 mg of the intermediate.

FAB-MS: m/z 479(65, $[M+H]^+$)

PMR (DMSO-d_6) δ: 10.11 (s, 3H), 9.97 (s, 1H), 9.80-9.60 (b.s., 2H), 8.50-8.00 (b.s., 3H), 7.40 (t, J=5.8 Hz, 1H), 7.25 (d, J=1.7 Hz, 1H), 7.19 (d, J=1.7 Hz, 1H), 7.08 (d, J=1.7 Hz, 1H), 7.06 (d, J=1.7 Hz, 1H), 6.94 (d, J=1.7 Hz, 1H), 6.88 (d, J=1.7 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.41 (m, 2H), 2.70 (m, 2H).

By analogous procedure and by using the opportune starting materials the following compounds can be obtained:
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminoimidazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propioncyanamidine hydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-3-aminopyrazole-5-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propioncyanamidine hydrochloride.

Step IV: The title compound

To a solution of 205 mg of the intermediate obtained from step III, 100 mg of $NaHCO_3$ in 40 ml of water and 20 ml of dioxane, a solution of 175 mg of the intermediate obtained from step II in 40 ml of dioxane was added. The solution was stirred for 2 hours at room temperature then the solvent was evaporated in vacuo and the crude residue was purified by flash chromatography (methylene chloride/methanol:10/1) to give 145 mg of the title compound as a white solid.

FAB-MS: m/z 734(90, $[M+H]^+$)

PMR (DMSO-d_6) δ: 11.00 (s, 1H), 10.47 (s, 1H), 9.99 (s,

1H), 9.90 (s, 1H), 8.80-8.00 (b.s., 3H), 7.35 (s, 1H), 7.30 (d, J=1.7 Hz, 1H), 7.24 (d, J=1.7 Hz, 1H), 7.19 (d, J=1.7 Hz, 1H), 7.08 (d, J=1.7 Hz, 1H), 7.03 (d, J=1.7 Hz, 1H), 6.87 (d, J=1.7 Hz, 1H), 6.79 (d, J=3.1 Hz, 1H), 6.31 (d, J=3.1 Hz, 1H), 4.04 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.40 (b.s., 2H), 2.80-2.30 (b.s., 2H).

By analogous procedure and by using the opportune starting materials the following compounds can be obtained:

(18) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propioncyanamidine

FAB-MS: m/z 734(95, $[M+H]^+$)

PMR (DMSO-d_6) δ: 10.52 (s, 1H), 10.12 (s, 1H), 9.94 (s, 1H), 9.90 (s, 1H), 8.80-8.00 (b.s., 3H), 7.52 (s, 1H), 7.26 (d, J=1.7 Hz, 1H), 7.23 (d, J=1.7 Hz, 1H), 7.18 (d, J=1.7 Hz, 1H), 7.14 (d, J=1.7 Hz, 1H), 7.04 (d, J=1.7 Hz, 1H), 6.87 (d, J=1.7 Hz, 1H), 6.80 (d, J=3.0 Hz, 1H), 6.30 (d, J=3.0 Hz, 1H), 3.97 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.60-3.20 (b.s., 2H), 2.80-2.30 (b.s., 2H);

(41) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propioncyanamidine;

(59) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propioncyanamidine;

(70) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propioncianamidine.

Example 2

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromo acrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido) pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-

methylamidine hydrochloride

Step I: The intermediate 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido] pyrrole-2-carboxamido]propion-N-methylamidine dihydrochloride

A solution of 2 g of distamycin A in 50 ml DMF was treated with 0.38 ml of methylamine hydrochloride 80%. After 8 hours additional 0.25 equivalents of methylamine hydrochloride 80% were added. The solution was evaporated to dryness and the crude residue was purified by flash chromatography (methylene chloride/methanol:8/2) to give 1.5 g of 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-formamidopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamidine hydrochloride which was dissolved in 40 ml of methanol and added with 5 ml of 2 N hydrochloric acid.

The reaction was stirred at room temperature for two days, the solvent evaporated in vacuo and the solid residue suspended in 200 ml of ethyl acetate, yielding after filtration 1.4 g of the intermediate.

FAB-MS: m/z 468 (40, $[M+H]^+$)

PMR (DMSO-d_6) δ: 10.20 (s, 3H), 10.18 (s, 1H), 9.98 (s, 1H), 9.65 (m, 1H), 9.20 (s, 1H), 8.63(s, 1H), 8.25 (t, J=5.8 Hz, 1H), 7.25 (d, J=1.7 Hz, 1H), 7.19 (d, J=1.7 Hz, 1H), 7.11 (d, J=1.7 Hz, 1H), 7.08 (d, J=1.7 Hz, 1H), 7.05 (d, J=1.7 Hz, 1H), 6.91 (d, J=1.7 Hz, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.79 (s, 3H), 3.60-3.40 (m, 2H), 2.80 (d, J=6 Hz, 3H), 2.61 (m, 2H).

By analogous procedure and by using the opportune starting materials the following compounds can be obtained:

3-[1-methyl-4-[1-methyl-4-[1-methyl-3-aminopyrazole-5-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propion-N-methylamidine dihydrochloride;

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminoimidazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propion-N-methylamidine dihydrochloride;

3-[1-methyl-5-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrazole-3-carboxamido] propion-N-methylamidine dihydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]imidazole-2-carboxamido] propion-N-methylamidine dihydrochloride.

Step II: The title compound

To a solution containing 0.20 g of the intermediate obtained from step I in 10 ml of dry DMF, 0.15 g of intermediate obtained from example I step I, 0.153 g of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride and 0.09 ml of N,N'-diisopropylethylamine were added. The mixture was stirred overnight at room temperature and brought to pH 4-5 with 10% hydrochloric acid.

After evaporation in vacuo of the solvent a solid residue was obtained which was purified by flash chromatography (methylene chloride/methanol:8/2) yielding 0.13 g of the title compound.

FAB-MS: m/z 723(95, $[M+H]^+$)

PMR (DMSO-d_6) δ: 11.02 (s, 1H), 10.48 (s, 1H), 10.00 (s, 1H), 9.92 (s, 1H), 9.52 (q, J=5.0 Hz, 1H), 9.12 (b.s., 1H), 8.56 (b.s., 1H), 8.22 (t, J=5.0 Hz, 1H), 7.35 (s, 1H), 7.31 (d, J=1.7 Hz, 1H), 7.24 (d, J=1.7 Hz, 1H), 7.18 (d, J=1.7 Hz, 1H), 7.09 (d, J=1.7 Hz, 1H), 7.06 (d, J=1.7 Hz, 1H), 6.93 (d, J=1.7 Hz, 1H), 6.80 (d, J=3.2 Hz, 1H), 6.31 (d, J=3.2 Hz, 1H), 4.00 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.49 (m, 2H), 2.78 (d, J=5.0 Hz, 3H), 2.59 (m, 2H).

By analogous procedure and by using the opportune starting materials the following compounds can be obtained:

(3) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine;

(19) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-

bromoacrylamido)imidazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine

FAB-MS: m/z 723(100, $[M+H]^+$)

PMR (DMSO-d_6) δ: 10.54 (s, 1H), 10.11 (s, 1H), 9.97 (s, 1H), 9.91 (s, 1H), 9.50 (b.s., 1H), 9.10 (b.s., 1H), 8.55 (b.s., 1H), 8.21 (t, J=5.6Hz, 1H), 7.52 (s, 1H), 7.26 (d, J=1.7 Hz, 1H), 7.23 (d, J=1.7 Hz, 1H), 7.17 (d, J=1.7 Hz, 1H), 7.16 (d, J=1.7 Hz, 1H), 7.06 (d, J=1.7 Hz, 1H), 6.92 (d, J=1.7 Hz, 1H), 6.80 (d, J=3.0 Hz, 1H), 6.30 (d, J=3.0 Hz, 1H), 3.97 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.49 (m, 2H), 2.78 (d, J=4.7Hz, 3H),2.58 (t, J=6.0Hz, 2H);

(32) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine;

(33) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine;

(46) 3-(1-methyl-3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrazole-5-carboxamido)propion-N-methylamidine;

(50) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)imidazole-2-carboxamido)propion-N-methylamidine;

(54) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine;

(60) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-

carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine;
(61) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine;
(71) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine.

Example 3

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromo acrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido) pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N'-dimethylamidine hydrochloride

Step I: The intermediate 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido] pyrrole-2-carboxamido]propion-N,N'-dimethylamidine dihydrochloride

A solution of 1.5 g of distamycin A in 40 ml DMF was heated to 80°C and treated with 4 ml of methylamine hydrochloride 80%. After 4 hours additional 5 equivalents (4 ml) of methylamine hydrochloride 80% were added. The solution was evaporated to dryness and the crude residue was purified by flash chromatography (methylene chloride/methanol:8/2) to yield 1.2 g of 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-formamidopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N'-dimethyl-amidine hydrochloride which was dissolved in 40 ml of methanol and added with 5 ml of 2 N hydrochloric acid solution.

The reaction was stirred at room temperature for two days, the solvent evaporated in vacuo and the solid residue suspended in 200 ml of ethyl acetate, yielding after filtration 1.4 g of the intermediate.

FAB-MS: m/z 482(45, $[M+H]^+$)

PMR (DMSO-d_6) δ: 10.21 (s, 3H), 10.18 (s, 1H), 9.98 (s, 1H), 9.61 (m, 1H), 8.85 (s, 1H), 8.39 (t, J=5.8 Hz, 1H),

8.00-7.70 (b.s., 1H), 7.28 (d, J=1.7 Hz, 1H), 7.22 (d, J=1.7 Hz, 1H), 7.12 (d, J=1.7 Hz, 1H), 7.08 (d, J=1.7 Hz, 1H), 7.03 (d, J=1.7 Hz, 1H), 6.92 (d, J=1.7 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.60-3.40 (m, 2H), 3.02 (d, J=6 Hz, 3H), 2.80 (d, J=6 Hz, 3H), 2.72 (m, 2H).

By analogous procedure and by using the opportune starting material the following compounds can be obtained:
3-[1-methyl-4-[1-methyl-4-[1-methyl-3-aminopyrazole-5-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propion-N,N'-dimethylamidine dihydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminoimidazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propion-N,N'-dimethylamidine dihydrochloride;
3-[1-methyl-3-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrazole-5-carboxamido] propion-N,N'-dimethylamidine dihydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]imidazole-2-carboxamido] propion-N,N'-dimethylamidine dihydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N,N,N'-trimethylamidine dihydrochloride
FAB-MS: m/z 482,(45, $[M+H]^+$)
PMR (DMSO-d_6) d : 10.21 (s, 3H), 10.18 (s, 1H), 9.61 (m, 1H), 8.85 (s, 1H), 8.39 (t, J=5.8 Hz, 1H), 8.00-7.70 (b.s., 1H), 7.28 (d, J=1.7 Hz, 1H), 7.22 (d, J=1.7 Hz, 1H), 7.12 (d, J=1.7 Hz, 1H) 7.08 (d, J=1.7 Hz, 1H), 7.03 (d, J=1.7 Hz, 1H), 6.92 (d, J=1.7 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.60-3.40 (m, 2H), 3.02 (d, J=6 Hz, 3H), 2.80 (d, J=6 Hz, 3H), 2.72 (m, 2H);
3-[1-methyl-4-[1-methyl-4-[1-methyl-3-aminopyrazole-5-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propion-N,N,N'-trimethylamidine dihydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminoimidazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propion-N,N,N'-trimethylamidine dihydrochloride.

Step II: The title compound

To a solution of 100 mg of the intermediate obtained from step I, 50 mg of $NaHCO_3$ in 10 ml of water, was added to a solution of 85 mg of the intermediate obtained from step II example 1 in 15 ml of benzene. The slurry was vigorously stirred for 1 hour at room temperature then the solvent was evaporated in vacuo and the crude residue was purified by flash chromatography (methylene chloride/methanol:8/2) to give 80 mg of the title compound as a white solid.

FAB-MS: m/z 737(95, $[M+H]^+$)

PMR (DMSO-d_6) δ: 11.02 (s, 1H), 10.47 (s, 1H), 9.99 (s, 1H), 9.92 (s, 1H), 9.40 (q, J=4.7 Hz, 1H), 8.65 (q, J=4.7 Hz, 1H), 8.27 (t, J=5.0 Hz, 1H), 7.34 (s, 1H), 7.30 (d, J=1.7 Hz, 1H), 7.23 (d, J=1.7 Hz, 1H), 7.18 (d, J=1.7 Hz, 1H), 7.08 (d, J=1.7 Hz, 1H), 7.06 (d, J=1.7 Hz, 1H), 6.93 (d, J=1.7 Hz, 1H), 6.79 (d, J=3.0 Hz, 1H), 6.32 (d, J=3.0 Hz, 1H), 4.04 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.45 (m, 2H), 3.00 (d, J=4.7 Hz, 3H), 2.77 (d, J=4.7 Hz, 3H),2.70 (t, J=6.6 Hz, 2H).

By analogous procedure and by using the opportune starting materials the following compounds can be obtained:

(20) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N'-dimethylamidine

FAB-MS: m/z 737(90, $[M+H]^+$)

PMR (DMSO-d_6) δ: 11.54 (s, 1H), 10.12 (s, 1H), 9.96 (s, 1H), 9.92 (s, 1H), 9.43 (q, J=5.0 Hz, 1H), 8.68 (q, J=4.7 Hz, 1H), 8.28 (t, J=4.9 Hz, 1H), 7.52 (s, 1H), 7.26 (d, J=1.7 Hz, 1H), 7.23 (d, J=1.7 Hz, 1H), 7.18 (d, J=1.7 Hz, 1H), 7.15 (d, J=1.7 Hz, 1H), 7.06 (d, J=1.7 Hz, 1H), 6.92 (d, J=1.7 Hz, 1H), 6.80 (d, J=3.0 Hz, 1H), 6.30 (d, J=3.0 Hz, 1H), 3.97 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.40 (m, 2H), 3.00 (d, J=4.7 Hz, 3H), 2.77 (d, J=5.0 Hz, 3H),2.71 (t, J=6.8 Hz, 2H);

(5) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N'-dimethylamidine;

(34) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N'-dimethylamidine;

(47) 3-(1-methyl-3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrazole-5-carboxamido)propion-N,N'-dimethylamidine;

(55) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N'-dimethylamidine;

(62) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N'-dimethylamidine;

(72) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N'-dimethylamidine;

(6) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N,N'-trimethylamidine;

(21) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N,N'-trimethylamidine;

(35) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-

carboxamido)propion-N,N,N'-trimethylamidine;

(63) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N,N'-trimethylamidine;

(73) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N,N'-trimethylamidine.

Example 4

2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromo acrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido) pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine hydrochloride

Step I: The intermediate 2-aminoethylguanidine dihydrochloride

A solution of commercial N-BOC-ethylendiamine (1 g) in dry ethanol (100 ml) and 2-methyl-2-thiopseudourea hydroiodide (1.5 g) was refluxed for 8 hours. The solvent was removed at reduced pressure and the crude residue purified by flash chromatography (methylene chloride/methanol:9/1) to yield 1.5 g of N-BOC-2-aminoethylguanidine hydroiodide as a yellow oil which was dissolved in methanolic hydrochloric acid solution 5N (20 ml) and stirred at room temperature for 3 hours. The white precipitate was collected, washed with dry ethanol, affording 700 mg of the intermediate.

FAB-MS: m/z 103(20, $[M+H]^+$)

PMR (DMSO-d_6) δ: 8.38 (b.s., 3H), 7.97 (t, J= 6 Hz, 1H), 7.51 (b.s., 4H), 3.45 (m, 2H), 2.92 (m, 2H).

Step II: The intermediate 2-[1-methyl-4[1-methyl-4[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido] pyrrole-2-carboxamido]ethylguanidine dihydrochloride

A solution of 1-methyl-4-[1-methyl-4-[1-methyl-4-

nitropyrrole -2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxylic acid (590 mg) (prepared as reported in Tetrahedron 34, 2389-2391, 1978) in 20 ml of DMF, 2-aminoethylguanidine dihydrochloride (500 mg), 1-hydroxybenzotriazole hydrate (350 mg), dicycloexylcarbodiimide (880 mg), and sodium bicarbonate (385 mg) was stirred at 70°C for 4 hours. The solution obtained after filtration was evaporated in vacuo and the residue purified by flash chromatography (methylene chloride/methanol:8/2) to yield 800 mg of 2-[1-methyl-4-[1-methyl-4-[1-methyl-4-nitropyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine hydrochloride, which was dissolved in methanol (100 ml), treated with 1N hydrochloric acid solution (2 ml) and reduced over Pd catalyst (10% on charcoal) under hydrogen atmosphere (50 psi) into a Parr apparatus. The solution obtained after filtration of the catalyst was evaporated in vacuo and the solid residue washed with dry ethanol to yield 750 mg of the intermediate as a brown powder.

FAB-MS: m/z 469(15, $[M+H]^+$)

PMR (DMSO-d_6) δ: 10.38-10.11 (b.s., 4H), 9.98 (s, 1H), 8.28 (b.s., 1H), 8.19 (d, J= 1.7 Hz, 1H), 7.73, (b.s., 1H), 7.63 (d, J= 1.7 Hz, 1H), 7.60-7.00 (b.s., 4H), 7.28 (d, J= 1.7 Hz, 1H), 7.20 (d, J= 1.7 Hz, 1H), 7.1 (d, J= 1.7 Hz, 1H), 6.92 (d, J= 1.7 Hz, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.82 (s, 3H), 3.28 (m, 4H).

By analogous procedure and by using the suitable starting materials the following compounds can be obtained:

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propioncyanamidine hydrochloride;

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminoimidazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propioncyanamidine hydrochloride;

3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]

propion-N-methylamidine dihydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-3-aminopyrazole-5-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propion-N-methylamidine dihydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propion-N,N'-dimethylamidine dihydrochloride;
3-[1-methyl-3-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrazole-5-carboxamido] propion-N,N'-dimethylamidine dihydrochloride;
3-[1-methyl-4[1-methyl-4[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamide hydrochloride;
3-[1-methyl-4[1-methyl-4[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]imidazole-2-carboxamido] propionamide hydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propion-N,N-dimethylamine dihydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminoimidazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propion-N,N-dimethylamine dihydrochloride;
3-[1-methyl-4[1-methyl-4[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionitrile hydrochloride;
2-[1-methyl-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine dihydrochloride;
2-[1-methyl-[1-methyl-3-aminopyrazole-5-carboxamido]pyrrole-2-carboxamido]ethylguanidine dihydrochloride;
2-[1-methyl-[1-methyl-4-aminoimidazole-2-carboxamido]pyrrole-2-carboxamido]ethylguanidine dihydrochloride;
2-[1-methyl-3[1-methyl-4[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrazole-5-carboxamido] ethylguanidine hydrochloride;
2-[1-methyl-4[1-methyl-4[1-methyl-4-aminopyrrole-2-

carboxamido]pyrrole-2-carboxamido]imidazole-2-carboxamido] ethylguanidine hydrochloride.

Step III: The title compound

A solution of 250 mg of 1-methyl-3-(a-bromoacrylamido) pyrrole-5-carboxyl chloride (prepared as reported in Example 1 step III) in 15 ml of benzene, was added to a solution of the intermediate obtained from step II (250 mg) and 82 mg of $NaHCO_3$ in 5 ml of H_2O. The solution was vigorously stirred for 8 hours at room temperature, then evaporated in vacuo and the crude residue was purified by flash chromatography (methylene chloride/methanol:8/2) to yield 220 mg of the title compound as a yellow solid.

FAB-MS: m/z, 723(45, $[M+H]^+$)

PMR (DMSO-d_6) d: 10.30 (s, 1H), 9.95 (s, 1H), 9.92 (s, 1H), 9.90 (s, 1H),8.10 (t, J=5.9 Hz, 1H), 7.56 (t, J=5.9, 1H), 7.34 (s, 1H) 7.2 (b.s., 4H), 7.23 (m, 3H), 7.19 (d, J=1.7 Hz, 1H), 7.04 (d, J=1.7Hz, 1H), 6.98 (d, J=1.7 Hz, 1H), 6.68 (d, J=2.9 Hz, 1H), 6.21 (d, J=2.9 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.30 (b.s., 4H).

By analogous procedure and by using the opportune starting materials the following compounds can be obtained:

(10) 2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine;

(24) 2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine;

(25) 2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-chloroacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine;

(37) 2-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine;

(38) 2-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine;

(48) 2-(1-methyl-3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-5-carboxamido)ethylguanidine;

(52) 2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)imidazole-2-carboxamido)ethylguanidine;

(56) 2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine;

(65) 2-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine;

(66) 2-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine;

(76) 2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine;

(11) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propyl-N,N-dimethylamine;

(26) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-

carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propyl-N,N-dimethylamine;

(43) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N-dimethylamine;

(77) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N-dimethylamine.

Example 5

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromo acrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido) pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamidoxime

***Step I*:** The intermediate 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido] pyrrole-2-carboxamido]propionamidoxime hydrochloride

1.2 g of 3-[1-methyl-4-[1-methyl-4-[1-metyhyl-4-nitropyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionitrile (prepared as reported in J.Med.Chem 22,1296-1301,1979) was suspended in dry ethanol and the solution saturated with dry hydrogen chloride. After 24 hours at room temperature, the solvent was evaporated under vacuo and the residue treated with two equivalents of solution of hydroxylamine in dry ethanol. After 24 hours at room temperature, the solvent was evaporated in vacuo and the residue purified by flash chromatography yielding 500 mg of 3-[1-methyl-4-[1-methyl-4-[1-methyl-4-nitropyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamidoxime which was dissolved in a mixture of methanol-dioxane-10% hydrochloric acid (4:1:1) and reduced over Pd catalyst (10% on charcoal) under hydrogen atmosphere (50 psi) into a Parr apparatus.

The solution obtained after filtration of the catalyst was evaporated in vacuo, and the solid residue suspended in dry ethanol, and filtered to yield 500 mg of the intermediate.
FAB-MS: m/z 480 (20, $[M+H]^+$)
PMR (DMSO-d_6) δ : 10.18 (b.s., 6H), 9.98 (s, 1H), 8.32 (t, J=5.7 Hz, 1H),7.25 (d, J=1.7 Hz, 1H), 7.20 (d, J=1.7 Hz, 1H), 7.16(d, J=1.7 Hz, 1H), 7.12 (d, J=1.7 Hz, 1H), 7.10 (d, J=1.7 Hz, 1H), 6.93 (d, J=1.7 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.82 (b.s., 7H), 3.50 (m, 2H), 2.72 (m, 2H).

By analogous procedure and by using the opportune starting materials the following compounds can be obtained:
3-[1-methyl-4-[1-methyl-4-[1-methyl-3-aminopyrazole-5-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamidoxime hydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminoimidazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propionamidoxime hydrochloride;
3-[1-methyl-3-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrazole-5-carboxamido] propionamidoxime hydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]imidazole-2-carboxamido] propionamidoxime hydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propion-N-methylamidoxime hydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]imidazole-2-carboxamido] propion-N-methylamidoxime hydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propion-N-methylamidine dihydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]imidazole-2-carboxamido] propion-N-methylamidine dihydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-3-aminopyrazole-5-

carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propion-N-methylamidine dihydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminopyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propioncyanamidine hydrochloride;
3-[1-methyl-4-[1-methyl-4-[1-methyl-4-aminoimidazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] propioncyanamidine hydrochloride.

Step II: The title compound
To a solution of 200 mg of the intermediate obtained from step I, 100 mg of $NaHCO_3$ in 40 ml of water and 20 ml of dioxane, a solution of 175 mg of the intermediate obtained from step II example I in 40 ml of dioxane was added. The solution was stirred for 2 hours at room temperature then the solvent was evaporated in vacuo and the crude residue was purified by flash chromatography (methylene chloride/methanol :9/1) to give 120 mg of the title compound as a white solid.
FAB-MS: m/z 724(50, $[M+H]^+$)
PMR (DMSO-d_6) δ : 10.28 (s, 1H), 9.97 (s, 1H), 9.93 (s, 1H), 9.92 (s, 1H), 9.80 (b.s., 2H), 8.32 (m, 1H), 7.35 (s, 1H), 7.25 (d, J=1.7 Hz, 1H), 7.20 (d, J=1.7 Hz, 1H), 7.16(d, J=1.7 Hz, 1H), 7.12 (d, J=1.7 Hz, 1H), 7.10 (d, J=1.7 Hz, 1H), 6.93 (d, J=1.7 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.82 (b.s., 7H), 3.40 (m, 2H), 2.64 (m, 2H).

By analogous procedure and by using the opportune starting materials the following compounds can be obtained:
(13) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamidoxime;
(27) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamidoxime;

(28) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-chloroacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamidoxime;

(39) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamidoxime;

(49) 3-(1-methyl-3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrazole-5-carboxamido)propionamidoxime;

(53) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)imidazole-2-carboxamido)propionamidoxime;

(57) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamidoxime;

(67) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamidoxime;

(68) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamidoxime;

(78) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamidoxime;

(14) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-O-methylamidoxime;

(15) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-

carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-O-methylamidoxime;

(29) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-O-methylamidoxime;

(30) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-chloroacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-O-methylamidoxime;

(44) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-O-methylamidoxime;

(79) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-O-methylamidoxime;

(70) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propioncianamidine;

(71) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine;

Example 6

3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-3(α-bromo acrylamido)pyrazole-5-carboxamido]pyrrole-2-carboxamido] pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionitrile

To a solution of 350 mg of 3-[1-methyl-4[1-methyl-4[1-methyl-4-[1-methyl-3(α-bromoacrylamido)pyrazole-5-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido] pyrrole-2-carboxamido]propionamidine hydrochloride (prepared as reported in WO 90/05196) in 20 ml of DMF, were added 120 mg of succinic anhydride and 165 mg of K_2CO_3. The

solution was heated at 60°C for 3 hours then the solvent evaporated under reduced pressure and the crude residue was purified by flash chromatography (methylene chloride/methanol:95/5) to yield 150 mg of the title compound as a pale yellow solid.

FAB-MS: m/z, 691(70, $[M+H]^+$)

PMR (DMSO-d_6) d: 11.02 (s, 1H), 10.48 (s, 1H), 10.00 (s, 1H), 9.92 (s, 1H), 8.21 (m, 1H), 7.35 (s, 1H), 7.30 (d, J=1.8 Hz, 1H), 7.24 (d, J=1.8 Hz, 1H), 7.17 (d, J=1.8 Hz, 1H), 7.09 (d, J=1.8 Hz, 1H), 7.06 (d, J=1.8 Hz, 1H), 6.79 (d, J=3.4 Hz, 1H), 6.31 (d, J=3.4 Hz, 1H), 4.04 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.42 (m, 2H), 2.75 (m, 2H).

By analogous procedure and by using the opportune starting materials the following compounds can be obtained:

(17) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionitrile;

(31) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionitrile;

(40) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionitrile;

(45) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionitrile;

(58) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionitrile;

(69) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionitrile;

(80) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionitrile;

Example 7

3-[1-methyl-4[1-methyl-4[1-methyl-3(α-bromoacrylamido) pyrazole-5-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide

Step I: The intermediate 3-[1-methyl-4[1-methyl-4[1-methyl-3-aminopyrazole-5-carboxamido]pyrrole-2-carboxamido] pyrrole-2-carboxamido]propionamide hydrochloride

To a solution of 200 mg of 3-(1-methyl-4(1-methyl-4-(1-methyl-3-nitropyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamidine hydrochloride (prepared as described in WO 96/05196) in 10 ml of acetonitrile and 10 ml of water, 2 ml of NaOH 1N were added. The solution was heated at 60°C for 4 hours then the solvent was evaporated in vacuo and the crude residue was purified by flash chromatography (methylene chloride/methanol:10/1) affording 175 mg of 3-(1-methyl-4(1-methyl-4-(1-methyl-3-nitropyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamide as a light yellow solid.

The nitro derivative (170 mg) was dissolved in a mixture of 20 ml of methanol-dioxane-10%hydrochloric acid (4:1:1) and reduced over Pd catalyst (10% on charcoal) under hydrogen pressure (50 psi) into a Parr apparatus. The solution obtained after filtration of the catalyst was evaporated to dryness giving a solid residue which was suspended in dry ethanol, and filtered to yield 150 mg of the intermediate as a white solid.

FAB-MS: 471 m/z, (60, $[M+H]^+$)

PMR (DMSO-d_6) d: 10.48 (s, 1H), 10.20 (s, 3H), 10.00 (s,

1H), 9.92 (s, 2H), 8.20 (m, 1H), 7.35 (s, 1H), 7.30 (d, J=1.8 Hz, 1H), 7.18 (s, 1H), 7.09 (d, J=1.8 Hz, 1H), 4.04 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.33 (m, 2H), 2.30 (m, 2H).

By analogous procedure and by using the opportune starting materials the following products can be obtained:
3-[1-methyl-4[1-methyl-4[1-methyl-4-aminoimidazole-4-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide.hydrochloride;
3-[1-methyl-4[1-methyl-4[1-methyl-3-aminopyrazole-5-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamide.hydrochloride;
3-[1-methyl-4[1-methyl-4[1-methyl-4-aminopyrrole-4-carboxamido]pyrrole-2-carboxamido]imidazole-2-carboxamido]propionamide.hydrochloride;
3-[1-methyl-4[1-methyl-4[1-methyl-4-aminopyrrole-4-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamide.hydrochloride;
3-[1-methyl-4[1-methyl-4[1-methyl-3-aminopyrazole-5-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propion-N-methylamide.hydrochloride;
3-[1-methyl-4[1-methyl-4[1-methyl-4-aminopyrrole-4-carboxamido]pyrrole-2-carboxamido]imidazole-2-carboxamido]propion-N-methylamide.hydrochloride.

Step II: The title compound

To a solution of 70 mg of α-bromoacrylic acid in 8 ml of DMF, 50 mg of dicyclohexylcarbodiimide were added. The solution was stirred at room temperature for 20' then added of 110 mg of the intermediate obtained from step I and 18 mg of $NaHCO_3$. The mixture was stirred at room temperature for 8 hours, the solvent evaporated in vacuo and the crude residue purified by flash chromatography (methylene chloride/methanol:9/1) to give 70 mg of the title compond as a white solid.
FAB-MS: m/z, 587(75, $[M+H]^+$)

PMR (DMSO-d_6) d: 10.30 (s, 1H), 10.27 (s, 1H), 9.98 (s, 1H), 9.92 (s, 2H), 8.20 (m, 1H), 7.30 (s, 1H), 7.30 (d, J=1.8 Hz, 1H), 7.20 (s, 1H), 7.09 (d, J=1.8 Hz, 1H), 6.66 (d, J=3.0 Hz, 1H), 6.20 (d, J=3.0 Hz, 1H), 4.04 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.33 (m, 2H), 2.30 (m, 2H).

By analogous procedure and by using the opportune starting materials the following compounds can be obtained:

(7) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamide

FAB-MS: m/z 709(60, $[M+H]^+$)

PMR (DMSO-d_6) δ: 11.02 (s, 1H), 10.48 (s, 1H), 10.00 (s, 1H), 9.92 (s, 1H), 9.50 (s, 2H), 8.22 (t, J=5.0 Hz, 1H), 7.35 (s, 1H), 7.31 (d, J=1.7 Hz, 1H), 7.24 (d, J=1.7 Hz, 1H), 7.18 (d, J=1.7 Hz, 1H), 7.09 (d, J=1.7 Hz, 1H), 7.06 (d, J=1.7 Hz, 1H), 6.93 (d, J=1.7 Hz, 1H), 6.80 (d, J=3.2 Hz, 1H), 6.31 (d, J=3.2 Hz, 1H), 4.00 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.40 (m, 2H), 2.50 (m, 2H);

(8) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamide;

(22) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamide;

(23) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamide

FAB-MS: m/z 723(80, $[M+H]^+$)

PMR (DMSO-d_6) δ: 11.54 (s, 1H), 10.12 (s, 1H), 9.96 (s, 1H), 9.92 (s, 1H), 9.40 (m, 1H), 8.25 (m, 1H), 7.52 (s,

1H), 7.26 (d, J=1.7 Hz, 1H), 7.23 (d, J=1.7 Hz, 1H), 7.18 (d, J=1.7 Hz, 1H), 7.15 (d, J=1.7 Hz, 1H), 7.06 (d, J=1.7 Hz, 1H), 6.92 (d, J=1.7 Hz, 1H), 6.80 (d, J=3.0 Hz, 1H), 6.30 (d, J=3.0 Hz, 1H), 3.97 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.30 (m, 2H), 3.00 (s, 3H), 2.28 (m, 2H);

(36) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamide;

(42) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamide;

(51) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)imidazole-2-carboxamido)propionamide;

(74) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamide;

(75) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamide;

(62) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N'-dimethylamidine;

(63) 3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N,N'-trimethylamidine;

(76) 2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine;

(77) 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N-dimethylamine.

Example 8

Intramuscular injection 10 mg/ml

An injectable pharmaceutical composition was manufactured by dissolving 10 g of 3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N-methylamidine in water for injection (1000 ml) and sealing ampoules of 1-5 ml.

Example 9

Capsules, each dosed at 0.200 g and containing 10 mg of the active substance were prepared as follows:

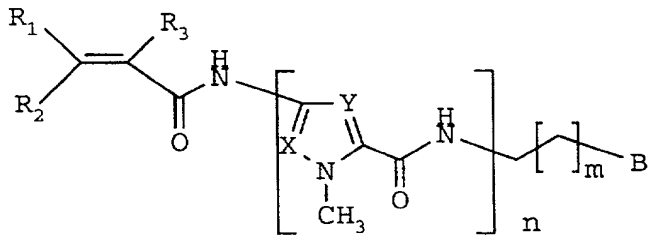
Composition for 500 capsules:

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromo acrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido) pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine hydrochloride	5 g
Lactose	85 g
Corn starch	5 g
Magnesium stearate	5 g

This formulation can be encapsulated in two-piece hard gelatin capsules and dosed at 0.200 g for each capsule.

CLAIMS

1. A compound which is an acryloyl substituted distamycin derivative of formula



(I)

wherein:

n is 2, 3 or 4;

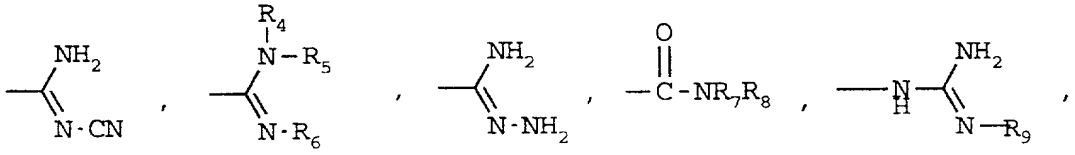
m is 1 or 2;

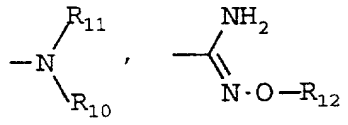
X and Y are the same or different and are selected, independently for each heterocyclic ring of the polyetherocyclic chain, from N and CH;

R_1 and R_2, which are the same or different, are selected from hydrogen, halogen, and C_1-C_4 alkyl;

R_3 is hydrogen or halogen;

B is selected from





and $-C\equiv N$;

wherein R_4, R_5, R_6, R_7, R_8, R_{10}, R_{11} and R_{12} are, independently from each other, hydrogen or C_1-C_4 alkyl; and R_9 is hydrogen or hydroxy;

or a pharmaceutically acceptable salt thereof;

provided that

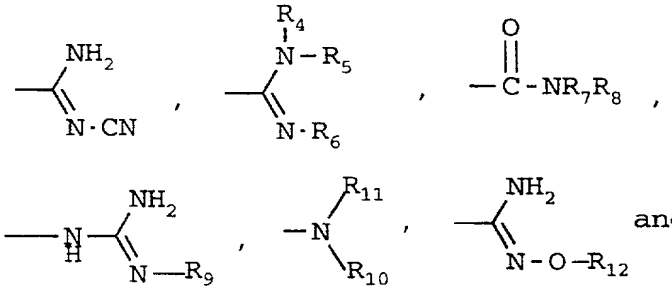
a) at least one of R_4, R_5 and R_6 is alkyl;

b) at least one of the heterocyclic rings within the polyheterocyclic chain is other than pyrrole; and

c) X and Y are not both N for the same heterocyclic ring.

2. A compound according to claim 1 wherein R_4, R_5, R_6, R_7, R_8, R_{10}, R_{11} and R_{12} are, independently from each other, hydrogen, methyl, or ethyl.

3. A compound according to claim 1 or 2 wherein
X and Y are as defined in claim 1;
n is 3 or 4;
m is 1;
R_1 and R_2 are hydrogen;
R_3 is chlorine or bromine;
B is selected from



wherein R_4, R_5, R_6, R_7, R_8, R_{10}, R_{11} and R_{12} are, independently from each other, hydrogen or methyl; R_9 is hydrogen.

4. A compound according to claim 1 wherein the acrylamido moiety is directly linked to a pyrazole or imidazole ring.

5. A compound selected from the group consisting of:
3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)-pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propioncyanamidine;
3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine;
3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-

carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N'-dimethylamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N'-dimethylamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N,N'-trimethylamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamide;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamide;

2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine;

2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propyl-N,N-dimethylamine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-

bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamidoxime;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamidoxime;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-O-methylamidoxime;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-O-methylamidoxime;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionitrile;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionitrile;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propioncyanamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N'-dimethylamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N,N,N'-trimethylamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido propionamide;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N-methylamide;

2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) ethylguanidine;

2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-chloroacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) ethylguanidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propyl-N,N-dimethylamine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propionamidoxime;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-chloroacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propionamidoxime;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)

propion-O-methylamidoxime;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-chloroacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-O-methylamidoxime;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propionitrile;

3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N-methylamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N-methylamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N,N'-dimethylamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N,N,N'-trimethylamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N-methylamide;

2-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) ethylguanidine;

2-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrazole-5-

carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) ethylguanidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propionamidoxime;

3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propionitrile;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propioncyanamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N-methylamide;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-N,N-dimethylamine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propion-O-methylamidoxime;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido) propionitrile;

3-(1-methyl-3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrazole-5-carboxamido)propion-N-methylamidine;

3-(1-methyl-3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-

bromoacrylamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrazole-5-carboxamido)propion-N,N'-dimethylamidine;

2-(1-methyl-3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrazole-5-carboxamido)ethylguanidine;

3-(1-methyl-3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrazole-5-carboxamido)propionamidoxime;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)imidazole-2-carboxamido)propion-N-methylamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)imidazole-2-carboxamido)propionamide;

2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)imidazole-2-carboxamido)ethylguanidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)imidazole-2-carboxamido)propionamidoxime;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N'-dimethylamidine;

2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamidoxime;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionitrile;

3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propioncyanamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N'-dimethylamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N,N'-trimethylamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamide;

2-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-

bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine;

2-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamidoxime;

3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-chloroacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamidoxime;

3-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)pyrazole-5-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionitrile;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propioncianamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N'-dimethylamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N,N'-trimethylamidine;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamide;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N-methylamide;

2-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)ethylguanidine;

3(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-N,N-dimethylamine;

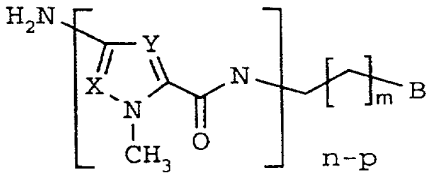
3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionamidoxime;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propion-O-methylamidoxime;

3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α-bromoacrylamido)imidazole-2-carboxamido)pyrrole-2-carboxamido)pyrrole-2-carboxamido)propionitrile; and the pharmaceutically acceptable salts thereof.

6. A process for preparing a compound as defined in claim 1, which process comprises:

(a) reacting a compound of formula:

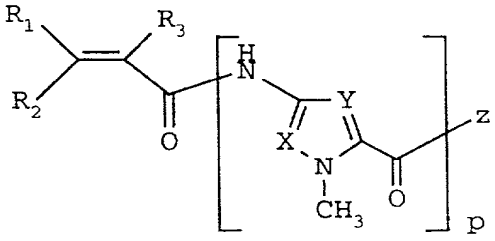


(II)

wherein n, m, X, Y and B are as defined in claim 1;

p is 0 or 1;

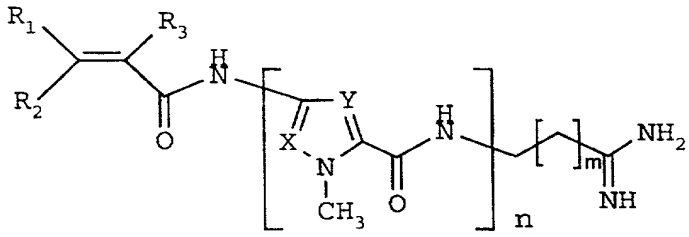
with a compound of formula:



(III)

wherein R_1, R_2, R_3, X and Y are as defined in claim 1;
p is as defined above;
Z is hydroxy or a leaving group;
or:

(b) when B is equal to -C≡N, reacting a compound of formula:



(IV)

wherein n, m, R_1, R_2, R_3, X and Y are as defined above;
with succinic anhydride; and,

(c) if desired, converting a compound of formula (I) into a pharmaceutically acceptable salt thereof.

7. A process according to claim 6 wherein, in the compound of formula (III), Z is a group selected from chloro, 2,4,5-tricholorophenoxy; 2,4-dinitrophenoxy, succinimido-N-oxy and imidazolyl.

8. A pharmaceutical composition comprising one or more pharmaceutically acceptable carriers and/or diluents and, as the active principle, a compound as defined in claim 1.

9. A compound as defined in claim 1 for use in a method of treatment of the human or animal body by therapy.

10. A compound as claimed in claim 9 for use as an antitumour agent.

11. Use of a compound as defined in claim 1 in the manufacture of a medicament for use as an antitumor agent.

N, M, M & O Docket No. _____ NIKAIDO, MARMELSTEIN, MURRAY & ORAM LLP

Declaration For U.S. Patent Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention **entitled**
(Insert Title) ACRYLOYL DERIVATIVES ANALOGOUS TO DISTAMYCIN, PROCESS FOR PREPARING THEM, AND THEIR USE AS ANTITUMOR AGENTS.
the specification of which

(Check one of blocks 1, 2 or 3. See note A on back of this page)

1. ☐ is attached hereto.
2. ☒ was filed on 17 MARCH 1999 as International PCT Application Serial No. PCT/EP99/01822 and was amended on _____ (if applicable).
3. ☐ was filed on _____ as U.S. Application Serial No. _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application for which priority is claimed:

(List prior foreign applications. See note B on back of this page)

(Number)	(Country)	(Day/Month/Year Filed)	Priority Claimed
9806689.7	GB	27 MARCH 1998	☒ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

(See Note C on back of this page) ☐ See attached list for additional prior foreign applications

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT International application(s) designating the United States of America listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT International filing date of this application:

(List prior U.S. Applications or PCT International applications designating the U.S.)

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

And I hereby appoint as principal attorneys David T. Nikaido, Reg. No. 22,663; Charles M. Marmelstein, Reg. No. 25,895; George E. Oram, Jr., Reg. No. 27,931; Robert B. Murray, Reg. No. 22,980; Martin S. Postman, Reg. No. 18,570; E. Marcie Emas, Reg. No. 32,131; Michael G. Gilman, Reg. No. 19,114, Douglas H. Goldhush, Reg. No. 33,125; Kevin C. Brown, Reg. No. 32,402; Monica Chin Kitts, Reg. No. 36,105; Sharon N. Klesner, Reg. No. 36,335; John R. Fuisz, Reg. No. 37,327; and Richard J. Berman, Reg. No. 39,107.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

(See Note D on back of this page)

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Full name of seventh joint inventor, if any _____
Inventor's signature _____ _____
Residence _____ Date
Citizenship _____
Post Office Address _____

Full name of eighth joint inventor, if any _____
Inventor's signature _____ _____
Residence _____ Date
Citizenship _____
Post Office Address _____

Full name of ninth joint inventor, if any _____
Inventor's signature _____ _____
Residence _____ Date
Citizenship _____
Post Office Address _____